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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,326	HOFFMAN ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-28,30,32,36 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28,30,32,36 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 1/29/2010, are acknowledged and entered. Claims 33-35 have been cancelled by Applicant. Claim 41 is newly added. Claims 26-28, 30, 32, 36, and 41 are pending and under examination.

Interview Summary

Examiner conducted a phone interview with Applicants and their representative on February 23, 2010. Discussion focused on the 35 U.S.C. 103 rejections set forth in the previous Office Action. The Examiner explained that Applicants have failed to demonstrate an unexpected result that is commensurate in scope with the claims. The Examiner further explained that Applicants would have to demonstrate that the claimed combinations are more effective than the individual agents and more effective than a combination of BSO and disulfiram, which was known in the art to provide synergistic anticancer activity.

The Examiner has held the instant application in abeyance for 2 months while awaiting a filing of a Declaration providing further experimental evidence of unexpected results. Applicants have not provided any further experimental evidence as of the mailing of this Office Action.

Applicants' claims, as amended, are drawn to treating tumors comprising malignant cancer cells having an operative retinoblastoma protein comprising systemically administering a drug comprising a combination of at least one of disulfiram or curcumin and at least one of BCNU or BSO, wherein a plurality of separate dosage units of the drug is administered in a cumulative amount of from 0.01 to 8 grams per day of at least one of disulfiram or curcumin (*i.e.*, E-increasing agent) as needed to continuously maintain a decreased [GSH]2/[GSSH] ratio in malignant cells and consequently continuously maintain a dephosphorylated state of the retinoblastoma protein in the cancer cells, and a minimum effective amount of at least one of BCNU or BSO (*i.e.*, enzyme deactivating agent) to cause regression of the tumor.

The Hoffman Declaration filed 11/5/2007 presents evidence that a combination of disulfiram, BSO, curcumin, and BCNU completely erradicates bladder tumors *in vivo* (Figure 1).

The Spetner Declaration filed 11/5/2007 presents in vitro data demonstrating the effects of various combinations of disulfiram, BSO, curcumin, and BCNU against breast cancer cells. In Figure 1, it is shown that the four drug combination (i.e., disulfiram, BSO, curcumin, and BCNU) is significantly more effective than combinations of only two or three drugs.

The Sampson Declaration filed 11/13/2007 demonstrates the effectiveness of a combination of disulfiram, BSO, curcumin, and BCNU against pancreatic and prostate cancer cells in vitro (Figure 3-6). Figure 7 demonstrates that the four agent combination is more effective than 2 or 3 agent combinations against bladder tumor cells.

Accordingly, claims limited to administration of the four agent combination of disulfiram, BSO, curcumin, and BCNU are unobvious over the prior art of record. However, instant claims 26-28, 30, and 32 are not limited to the specific four agent combination of disulfiram, BSO, curcumin, and BCNU. Accordingly, the 35 U.S.C. 103 rejections over these claims are maintained for the reasons of record and as reiterated below.

Response to Arguments

Any previous rejections and/or objections to claims 33-35 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments, filed 1/29/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

As discussed supra, Applicants' claims, as amended, are drawn to treating tumors comprising malignant cancer cells having an operative retinoblastoma protein comprising systemically administering a drug comprising a combination of at least one of disulfiram or curcumin and at least one of BCNU or BSO, wherein a plurality of separate dosage units of the drug is administered in a cumulative amount of from 0.01 to 8 grams per day of at least one of disulfiram or curcumin (*i.e.*, E-increasing agent) as needed to continuously maintain a decreased [GSH]2/[GSSH] ratio in malignant cells and consequently continuously maintain a

dephosphorylated state of the retinoblastoma protein in the cancer cells, and a minimum effective amount of at least one of BCNU or BSO (*i.e.*, enzyme deactivating agent) to cause regression of the tumor.

The instant claims are replete with descriptive matter that does not limit the claims in any way. For example, recitation of "*...by dephosphorylizing the RB protein in said cancer cells and continuously maintaining a dephsophorylated state of the RB in said cancer cells to induce apoptosis thereof...*" in the preamble of the claims merely describes the intended effect of the claimed method, but does not limit the claims.

Another example of such descriptive matter is found in the phrase, "*...to cause an increase in intracellular redox potential (E)and decrease in the [GSH]2/[GSSG] (wherein [GSH] is the concentration of glutathione and [GSSG] is the concentration of glutathione disulfide) ratio in the malignant cancer cells of said tumor..*". This wording only describes the intended effect of the administration recited in the claims but also does not limit the claims in any way.

Instant claim 26, with purely descriptive material left out would read:

> A method of treating a tumor in a patient, said tumor comprising malignant cancer cells having an operative retinoblastoma protein (RB), comprising the steps of:
>
> systemically administering to said patient in need thereof a pharmaceutically effective dosage of a drug comprising a combination of at least one E-increasing agent from the group of disulfiram and curcumin, and at least one enzyme deactivating agent from the group of bis-chloronitrosourea (BCNU and buthionine sulfoximine (BSO);
>
> said pharmaceutically effective dosage of said drug further comprising a plurality of separate units of said drug administered in a cumulative amount of from 0.01-8 grams per day of said E-increasing agent as needed to continuously maintain said decreased [GSH]2/[GSSH] ratio in the malignant cells and consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle, and a minimum effective amount of said enzyme deactivating agent to cause regression of said tumor.

The only limitations that need to be taught or suggested by the prior art are administration of a cumulative amount of 0.01 to 8 grams per day of disulfiram and/or curcumin and BCNU and/or BSO, wherein the administration of the disulfiram and/or curcumin is administered to maintain a decreased [GSH]2/[GSSH] ratio in the malignant cells within a range of from 15 to 75 hours, and the BCNU and/or BSO is administered in an effective amount to cause regression of the tumor.

Declaration under Rule 1.132

The Examiner acknowledges receipt of the Rule 1.132 Declaration of Arnold Hoffman ("Hoffman" Declaration) and has carefully considered the information provided therein. Declarant states that the present inventor's solution is to use a combination of "two E-increasing agent" and "two enzyme deactivating agents" administered periodically. However, instant claims 26-28, 30, and 32 are not limited to the specific four agent combination of disulfiram, BSO, curcumin, and BCNU. The Declaration provides a Summary of the Protocol used for testing of systemic administration of the four agent combination of disulfiram, BSO, curcumin, and BCNU. However, no results are provided therein.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-28, 30, 32, 36, and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal

Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. This is a new matter rejection.

Amended claims 26 and 36 and newly added claim 41 recite the limitations:

"a plurality of separate dosage units of said drug administered in a cumulative amount of from 0.01-8 grams per said of said ***E-increasing agent*** *as needed*" (claims 26 and 36) and *"periodically within a range of from 1-8 grams per day*" (claim 41).

The only disclosure of separate dosage units is found in [0080] of the published patent application (U.S. 2004/0018987), wherein Applicants disclose that when a combination of two or more agents are used the invention preferably comprises a pharmaceutically effective package having at least one, and preferably two, or three, or four or more separate dosage units of different $[GSH]^2/[GSSG]$-**decreasing agents**. According to Applicants' disclosure, E-increasing agents and $[GSH]^2/[GSSG]$-decreasing agents are distinct agents ([0073]).

Accordingly, there is no support in the instant specification for administering an E-increasing agent in a plurality of separate units. Similarly, claim 41 recites periodic administration of disulfiram, curcumin, BCNU, and BSO within a range of 1-8 grams per day. However, the only disclosure in the specification of 1-8 grams per day relates to administration of **$[GSH]^2/[GSSG]$-decreasing agents**, not E-increasing agents such as disulfiram and curcumin.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The 35 U.S.C. 103(a) rejection of claims 26 and 32 as being unpatentable over **Cen *et al.*** (Molecular Cancer Therapeutics, January 2002, vol. 1, pages 197-204) in view of **Bailey *et al.*** (Journal of the National Cancer Institute, 1997, vol. 89, pages 1789-1796) is **withdrawn** in light of Applicants' arguments.

Claims 26 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Ali-Osman *et al.*** (Mol. Pharm., 1996, vol. 49, pages 1012-1020) and **Marikovsky** (USP No. 6,288,110; Issued Sep. 11, 2001) in view of **Bailey *et al.*** (Journal of the National Cancer Institute, 1997, vol. 89, pages 1789-1796).

Ali-Osman *et al.* disclose that depletion of GSH by BSO in human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract), thus motivating the use of BSO and BCNU together as recited in claims 26, 30, and 32. It is noted that BCNU is an agent that causes inhibition of the glutathione reductase enzyme. Figure 1 demonstrates that GCS is significantly inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell lines to treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column). The reference further suggests 24-hour exposure to BSO to decrease glutathione content in glioma cells (Abstract; Fig. 5). Ali-Osman *et al.* thus suggest and motivate the combined use of BSO and BCNU to treat tumors, especially in view of the teachings therein where *in vitro* and ***in vivo*** studies and clinical trials in humans have shown GSH depletion with BSO to be a potentially useful strategy with which to biochemically enhance the efficacy of cancer chemotherapy (page 1016, right column, "Discussion").

Marikovsky teaches administration of disulfiram to treat angiogenesis-dependent disorders such as neoplasms (Abstract). Examples of solid tumors that can be treated with

disulfiram include bladder, breast, cervix, ear, esophogus, kidney, larynx, liver, lung, ovary, pancreas, prostate, skin, stomach, thyroid, urethra, and uterus carcinomas (col. 3, lines 1-5).

Marikovsky teaches administration of disulfiram of 1 mL of an aqueous solution comprising 0.1-0.5 mM disulfiram (25-120 mg) to mice bearing C6 glioma tumors (col. 6, lines 54-63; Table 1). Marikovsky further teaches that disulfiram induces apoptosis of endothelial cells (Figure 4). 25-120 mg of disulfiram meets the limitation "cumulative amount of from 0.01-8 grams per day" as recited in amended claim 26.

Bailey *et al.* teach that increased intracellular glutathione has long been associated with tumor cell resistance to various cytotoxic agents (Abstract). BSO has been shown to enhance the cytotoxicity of chemotherapeutic agents *in vitro* and *in vivo* (*id.*). The authors studied the effects of BSO combined with melphalan in patients with advanced cancers. BSO was administered by continuous infusion on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours; 2) 0.75 g/m^2 per hour for 48 hours; 3) 0.75 g/m^2 per hour for 72 hours; or 4) 1.5 g/m^2 per hour for 48 hours (Abstract). The treatment method produced "consistent, profound glutathione [GSH] depletion" (id.; Figure 1; Figure 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered BCNU and/or BSO in combination with disulfiram to a subject having cancer, especially gliomas. The skilled artisan would have been motivated to do so because treatment with BSO has been shown in increase the cytotoxicity of glioma cells to BCNU and disulfiram is suggested in the prior art to be useful as a chemotherapeutic agent and has demonstrated *in vivo* efficacy also against glioma tumors. Furthermore, Bailey *et al.* teach that administration of BSO to human patients on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours; 2) 0.75 g/m^2 per hour for 48 hours; 3) 0.75 g/m^2 per hour for 72 hours; or 4) 1.5 g/m^2 per hour for 48 hours produced "consistent, profound glutathione [GSH] depletion".

In the absence of evidence to the contrary, the glioma cells treated in Ali-Osman *et al.*, the cancers listed in Marikovsky *et al.* (including C6 glioma tumors), and the cancers treated in Bailey *et al.* have an "operative retinoblastoma protein" as recited in the instant claims. For example, Applicants teach that human RB protein is expressed in "every tissue type examined" (page 2, lines 28-29), plays a major role in a regulatory circuit in late G_1 (growth) phase (*id.* at lines 29-30), and is involved in regulating an elusive switch point between cell cycle,

differentiation, and apoptosis (page 3, lines 3-4). As such, all cells in a subject would be expected to have an operative retinoblastoma protein. The effect recited in the instant claims (*i.e.*, dephosphorylizing the RB protein and maintaining a dephosphorylated state of the RB to induce apoptosis) would be a natural result of contacting glioma cells in a subject with BSO, BCNU, and disulfiram as suggested and motivated by the prior art. In fact, Bailey *et al.* teach that BSO administered to human patients on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours; 2) 0.75 g/m^2 per hour for 48 hours; 3) 0.75 g/m^2 per hour for 72 hours; or 4) 1.5 g/m^2 per hour for 48 hours produced "consistent, profound glutathione [GSH] depletion". Applicant's recognition of the mechanism through which BSO and BCNU induce apoptosis of glioma cells is not a patentable distinction over the treatment method taught in the cited prior art.

Response to Arguments

Applicant traverses the previous rejection, stating that Ali-Osman suggests the combination of BSO and BCNU. Applicant admits that Marikovsky teaches that administering disulfiram once per day will inhibit angiogenesis, but argues that the Examiner fails to explain how this translates to tumor cell apoptosis. Marikovsky teaches, suggests, and motivates the use of disulfiram to treat tumors, including gliomas. Ali-Osman et al. teaches that BSO and BCNU are effective in the treatment of glioma cells. Bailey et al. teach that BSO has been shown to enhance the cytotoxicity of chemotherapeutic agents *in vitro* and *in vivo*. As such, the skilled artisan would expect that administration of a combination of disulfiram, BSO, and BCNU (or disulfiram and BSO) would be effective to treat tumors, especially gliomas.

Applicants argue that the teachings of the cited prior art do not "add up" to Applicant's claimed administration of "disulfiram, curcumin, BCNU and BSO", especially in light of the synergistic in vivo effect established by Applicant. In response, the Examiner respectfully submits that the rejected claims do not require administration of "disulfiram, curcumin, BCNU and BSO". The rejected claims only require administration of disulfiram and BSO and/or BCNU.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Claims 26, 30, and 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **U.S. Patent No. 6,589,987** (Issued July 8, 2003; Filed Sept. 8, 1999) in view of **Nagendra *et al.*** (Alcohol, 1994, vol. 11, pages 7-10), **Huang *et al.*** (The FASEB Journal, 2001, vol. 15, pages 19-21; published online 11/9/2000), **Ali-Osman *et al.*** (Mol. Pharm., 1996, vol. 49, pages 1012-1020), and **Hoffman *et al.*** (J. Theor. Biol., 2001, vol. 211, pages 403-407).

USP '987 discloses that disulfiram inhibits the growth of cancer cells (Abstract; col. 2, lines 38-44). Disulfiram can also be administered in combination with another anticancer agent (col. 3, lines 10-13 and col. 7, lines 8-18). '987 thus suggests administering disulfiram to treat tumors as recited in claims 26, 30, and 32.

Nagendra *et al.* disclose that chronic administration of disulfiram to rats affects GSH metabolism (Abstract). Administration of disulfiram led to a decrease in GSH with a concomitant increase in GSSG content, which would thus result in a decrease in the $[GSH]^2/[GSSG]$ ratio as instantly claimed. Brain glutathione reductase activity was also significantly depleted. The authors conclude that treatment with disulfiram decreases GSH content with a concomitant increase in GSSG level and perturbs the GSH/GSSG redox status, inducing oxidative stress on the brain. As Nagendra *et al.* is cited only for this general teaching, it follows that it is silent with respect to treating tumors.

Huang *et al.* disclose that the glutathione (GSH) level in hepatocytes increases during active proliferation (Abstract). The authors evaluated whether a similar increase is found in hepatocellular carcinoma (HCC). It is disclosed that GSH levels doubled in HCC as compared to normal liver (page 19). HepG2 liver cancer cells were grown with varying concentrations of cysteine and it was found that cell growth increased with increasing cysteine concentration (page 19, right column). Further, BSO treatment decreased GSH levels and rates of growth. Cells treated with BSO for 24 hours had significantly lower DNA synthesis than controls (page 19, right column). The authors disclose that GSH has been found to be elevated in a number of drug-resistant tumor cell lines including prostate, ovarian, lung and colorectal cancers (page 20, right column), thus suggesting that a decrease is GSH as achieved with BSO may result in a decrease in cell growth. Increased γ-L-glutamyl-L-cysteine synthetase (GCS) activity was found in the majority of these resistant tumor cells. The authors conclude that "an increase in the cellular GSH content may change the thiol-redox status of the cell that is proportional to

$[GSH]^2/[GSSG]$" (page 21, right column). This change in redox state may then "affect the expression or activity of factors important for cell cycle progression". It is noted that BSO is recited as an agent that causes inhibition of the GCS enzyme (see instant claim 35). Huang *et al.* thus suggest and motivate the treatment of tumors having elevated GSH content as recited in instant claims 26 and 32.

Ali-Osman *et al.* disclose that depletion of GSH by BSO (currently being explored as a means of enhancing the efficacy of cancer chemotherapy and explicitly taught in Huang *et al.*) in human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract), thus motivating the use of BSO and BCNU together as for the treatment of cancer. It is noted that BCNU is an agent that causes inhibition of the glutathione reductase enzyme (see instant claim 33). Figure 1 demonstrates that GCS is significantly inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell lines to treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column). Ali-Osman *et al.* thus suggest and motivate the combined use of BSO and BCNU to treat tumors. The tertiary reference is silent with respect to disulfiram.

Hoffman *et al.* is cited for the general teaching that an elevated redox potential has been observed to be associated with the inability of retinoblastoma (RB) protein to be phosphorylated and with cell cycle arrest. As such, the authors suggest that an elevated redox potential can inhibit phosphorylation of RB protein, which in turn will stop cell proliferation (page 403, paragraph bridging left and right columns), thus suggesting the treatment of cancers having an operative retinoblastoma (RB) protein *via* changes in redox potential. Hoffman *et al.* further teach that application of agents that decrease GSH will increase redox potential (page 405, right column, second paragraph under the heading "Model"). For example, Hoffman *et al.* teach that addition of BSO (which is taught by Huang *et al.* to decrease GSH) to fibroblasts and fibrosarcoma cells results in a threshold potential of between -196 and -218 mV that resulted in cessation of cell proliferation (page 406, left column, first paragraph under the heading "Application of the Model to Interpreting Published Data).

In view of the above disclosures, the instant claims would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. It is well known in the art that administration of BSO depletes GSH content and enhances the cytotoxicity of BCNU. Further, disulfiram has been shown to inhibit cancer cell proliferation and decrease GSH with a concomitant increase in GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in instant claim 26). It would have been obvious to combine disulfiram, BSO and/or carmustine (BCNU) to treat tumors because from the disclosures of the '987 patent, Huang *et al.*, Ali-Osman *et al.* and Nagendra *et al.* it is clear that disulfiram is effective at inhibiting cancer cell proliferation and that decreasing GSH cell content has a significant effect on the cytotoxicity of the chemotherapeutic drug BCNU. Thus, the skilled artisan would be imbued with at least a reasonable expectation that administering disulfiram would decrease GSH, increase GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in the instant claims), and be an effective treatment for tumors. In addition co-administration of BSO would be predicted to further decrease GSH content resulting in the sensitization of tumors to BCNU treatment.

Although ample motivation to combine the references is found in the teachings of the individual references as discussed *supra*, difulfiram and carmustine (*i.e.* BCNU) are individually known in the art as agents for treating cancers, whose efficacy when administered alone is well established for the treatment of a large number of neoplasias and metastasis. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption. Further, the addition of BSO to a

composition of disulfiram and BCNU would have been obvious given the teachings of Ali-Osman *et al.* who disclose that BSO enhances the anticancer activity of BCNU.

Response to Arguments

Applicants' arguments have been carefully considered but they are not deemed to be persuasive. Applicants argue that Kennedy suggest thiuram disulfide (i.e., disulfiram) and a heavy metal ion can be administered in combination with another anticancer agent, but never suggests what the other agent might be. In response, the Examiner respectfully submits that the general teaching of administering disulfiram with another anticancer agent reasonably suggests that any known anticancer agent can be administered in combination with disulfiram.

Applicants argue that Nagendra suggests that disulfiram decreases GSH2/GSH but is silent with respect to treating tumors. In response, it is the teachings of Kennedy that suggest treating tumors with disulfiram. Further, Huang et al. teach that GSH is elevated in many tumors, thus motivating one skilled in the art to administer an agent that decreases GSH to treat tumors. In fact, Huang et al. demonstrate that an agent that decreases GSH (i.e., BSO) decreases the rate of growth of liver cancer cells.

Applicants argue that Hoffman et al. teaches that selectivity requires that the E of the normal cells be below the threshold to prevent their death, which limits the treatment to administering agents directly into tumor tissue to avoid contact of the normal cells with the E-increasing/maintaining agents. This argument is not persuasive because nowhere in Hoffman et al. is it taught that systemic administration should be avoided.

Applicants argue that the mechanism through which Applicants achieve their results is pertinent to the present rejection because the mechanism accounts for the action of GR and/or the gamma-GCS enzymes in vivo, and deactivates the GR and/or the gamma-GCS enzymes. This argument is not persuasive because the instant claims only require administration of a cumulative amount of 0.01 to 8 grams per day of disulfiram and/or curcumin and BCNU and/or BSO, wherein the administration of the disulfiram and/or curcumin is administered to maintain a decreased [GSH]2/[GSSH] ratio in the malignant cells within a range of from 15 to 75 hours, and the BCNU and/or BSO is administered in an effective amount to cause regression of the tumor. The cited prior art teaches, suggests, and motivates administering disulfiram in combination with

another anticancer agent to treat tumors and further teaches, suggests, and motivates the use of BSO and/or BCNU to treat tumors. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer disulfiram in combination with BSO and/or BCNU to treat tumors.

Regarding Applicants' argument that they have presented factual evidence supporting their proposition that "the combination of the four agents claims in claims 26, 30, and 32" provide in vivo synergy, the Examiner respectfully submits that claims 26, 30, and 32 do not require a "combination of four agents" as asserted by Applicants. The rejected claims only require, for examples, a combination of disulfiram and BSO.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Claims 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over **U.S. Patent No. 6,589,987** in view of **Nagendra *et al.***, **Huang *et al.***, **Ali-Osman *et al.***, and **Hoffman *et al.*** as applied to claims 26, 30, and 32 above, and further in view of **Ramachandran *et al.*** (Breast Cancer Research and Treatment, 1999, vol. 54, pages 269-278) and **Sharma *et al.*** (Clinical Cancer Research, July 2001, vol. 7, pages 1894-1900).

USP 6,589,987, Nagendra *et al.*, Huang *et al.*, Ali-Osman *et al.*, and Hoffman *et al.* teach as applied to claims 26, 30, and 32 above and are herein applied for the same teachings in their entirety. Claims 27-28 and 36-40 differ from USP 6,589,987, Nagendra *et al.*, Huang *et al.*, Ali-Osman *et al.*, and Hoffman *et al.* in that the cited references do not teach curcumin.

However, Ramachandran *et al.* teach that administration of curcumin to breast cancer cells induced apoptosis in breast cancer cells compared to a very low percentage of apoptosis in mammary epithelial cells (Abstract).

Sharma *et al.* teach that curcumin has been shown to prevent cancer of the skin, forestomach, duodenum, and colon of mice and in the tongue, colon, mammary glands, and sebaceous glands of rates. Curcumin was also known to be associated with the regression of established malignancies in humans (page 1894, right column). Sharma et al. teach administration of capsules containing Curcuma extract which contained 36, 72, 108, 144, or 180 mg of curcumin to human patients having colon cancer daily for 29 days (Abstract; Table 1; page

1895, paragraph briding left and right columns). Five patients exhibited stable disease on CT scan (page 1897, right column).

It would have been *prima facie* obvious to one of ordinary skill in the art to administer curcumin in combination with disulfiram, BCNU, and/or BSO to treat cancer in a subject. The skilled artisan would have been motivated to do so because curcumin has been taught to selectively induce apoptosis of breast cancer cells versus normal breast epithelial cells as well as to provide a clinical benefit in patients with colon cancer, and disulfiram, BCNU, and BSO have all been individually taught in the prior art to be effective antitumor agents alone and in combination with other chemotherapeutic agents. As such, it would have been obvious to one skilled in the art that curcumin combined with one or more of disulfiram, BCNU, and BSO would be effective to treat tumors in a subject.

Response to Arguments

Applicants' arguments have been carefully considered but they are not deemed to be persuasive. Applicants argue that the Examiner's rejection is a piecemeal combination of prior art that ignores the unique type in vivo synergistic effect of Applicant's specific combination of agents and specific regimen. In response, the Examiner respectfully submits that an in vivo synergistic effect has only been demonstrated for the four agent combination of disulfiram, curcumin, BSO, and BCNU. Claims that require such a four agent combination are not included in this rejection.

Applicants further argue that Sharma et al. did not show that the curcumin actually helped the patients or shrunk the cancer. This argument is not persuasive because Sharma et al. explicitly teach administration of capsules containing Curcuma extract which contained 36, 72, 108, 144, or 180 mg of curcumin to human patients having colon cancer daily for 29 days (Abstract; Table 1; page 1895, paragraph briding left and right columns) wherein five patients exhibited stable disease on CT scan (page 1897, right column). That Sharma et al. did not measure the shrinkage of cancer is not pertinent to the present rejection. The doses of curcumin administered fall within Applicants' claimed "cumulative amount of from 0.01-8 grams per day". Applicants have presented no factual evidence that daily administration of 36, 72, 108, 144, or

180 mg of curcumin to a patient having cancer does not have the effects recited in the instant claims.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Claims 26-27, 30, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Hoffman** (WO 02/056823; Published July 25, 2002) in view of **Ali-Osman *et al.*** (Mol. Pharm., 1996, vol. 49, pages 1012-1020) and **Cen *et al.*** (Molecular Cancer Therapeutics, January 2002, vol. 1, pages 197-204).

Hoffman teaches a method of treating malignancies through control of the redox state or environment of the cell, comprising administering a GSH-decreasing agent (Abstract). Treatment of tumors is taught at page 7, lines 25-32. The treatment of tumors having an operative RB protein as recited in claim 26 is taught at page 7, lines 22-24.

GSH depleting agents include oxidizers of GSH (*e.g.*, α-lipoic acid, hydrogen peroxide, ascorbic acid, quinones), agents that form adducts with GSH (*e.g.,* Michael acceptors), and inhibitors of GSH (*e.g.*, BSO) (pages 9-10).

Hoffman further teaches combinations comprising more than one GSH-depleting agent as recited in the instant claims (page 13, line 10 to page 14, line 6; page 16, line 5 to page 17, line 18; page 19, lines 11-33).

Hoffman teaches use of a composition of one or more GSH-decreasing agents wherein at least one of the agents is selected from foods, spices, and vitamins, preferably curcumin as recited in the instant claims (page 18, lines 27-31).

Hoffman teaches that conventional anticancer agents can be combined with GSH-depleting agents, including BCNU as recited in the instant claims (Table 1a).

Ali-Osman *et al.* disclose that depletion of GSH by BSO in human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract), thus motivating the use of BSO and BCNU together as recited in claims 26, 30, and 32. It is noted that BCNU is an agent that causes inhibition of the glutathione reductase enzyme. Figure 1 demonstrates that GCS is significantly inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell lines to

treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column). The reference further suggests 24-hour exposure to BSO to decrease glutathione content in glioma cells (Abstract; Fig. 5). Ali-Osman *et al.* thus suggest and motivate the combined use of BSO and BCNU to treat tumors, especially in view of the teachings therein where *in vitro* and ***in vivo*** studies and clinical trials in humans have shown GSH depletion with BSO to be a potentially useful strategy with which to biochemically enhance the efficacy of cancer chemotherapy (page 1016, right column, "Discussion").

Cen *et al.* teach that redox regulation in melanoma cells is aberrant and that disulfiram induces apoptosis of metastatic melanoma cells at a dose of 25-50 ng/mL (Abstract; Fig. 1; Fig. 2). BSO, an inhibitor of γ-glutamyl-cysteine synthetase, as a single agent also increased apoptosis and slightly enhanced the level of apoptosis induced by disulfiram when co-administered for 3 or 4 days (Abstract; Table 1). The authors teach that BSO depletes intracellular glutathione and disulfiram reduces the ratio of reduced and oxidized glutathione (Abstract; Table 2). GSH depletion by BSO was known in the art to enhance the cytotoxic effects of 1,3-bis(2-chloroethyl)-1-nitrosourea, cisplatin, and melphalan, to inhibit DNA synthesis or growth of melanoma cell lines *in vitro*, and to prolong the survival of melanoma-bearing mice after *in vivo* administration (page 197, right column). BSO alone causes significant apoptosis in tumor cells, especially neuroblastoma (*id.*).

In view of the cited prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the claimed active agents to treat tumors having an operative retinoblastoma protein. Hoffman explicitly suggests such combinations and further suggests that these combinations can be combined with other anticancer agents. Disulfiram was known in the art to decrease GSH and is thus an agent clearly encompassed by the teachings of Hoffman. BSO was known to increase the apoptosis induced by disulfiram, and BCNU was likewise known to be potentiated by BSO. As such, the skilled artisan would clearly expect that combinations of disulfiram, BCNU, and BSO, optionally further combined with curcumin as suggested and motivated by Hoffman, would be effective to treat tumors.

Response to Arguments

Applicants' arguments have been carefully considered but they are not deemed to be persuasive. Applicants argue that Hoffman incorrectly teaches that the treatment will only be selective if the E of the normal cells is not high enough to dephosphorylate the RB. This is not persuasive because Hoffman explicitly teaches that "[T]he approach of the present invention has a built-in selectivity. As normal proliferating cells generally have a lower E value, that is, more GSH than cancer cells (e.g. Hutter et al.), adding a limited amount of GSH-decreasing agents to a tissue containing a tumor can increase the E of the cancer cells to Eccp or beyond, whereas the E value of normal proliferating cells in the tissue can still remain lower than Eccp, as described previously" (page 8, lines 18-23). While the subject application may disclose that the redox therapy is selective even if the E of both the normal and cancer cells is high enough to dephosphorylate the RB, such is not required by the instant claims. The instant claims only require administration of the claimed active agents to a tumor comprising malignant cells having an operative RB protein.

Regarding Applicants' arguments that Hoffman do not suggest systemic administration, Hoffman clearly teaches and suggests systemic administration wherein it is disclosed that the administration of the compositions of the invention may be effected by any of the well-known methods of administration, including intravenous, intraperitoneal, oral, buccal, etc. (page 15, lines 19-24).

Regarding doses, Hoffman discloses that GSH-decreasing agents are administered in amounts from 0.1 to 50 mg/kg per day, which is well within the claimed 0.01-8 grams per day. Hoffman even explicitly teaches an adult dose as much as 2 grams per day or more (page 15, lines 13-18).

Regarding the claimed maintenance of the dephosphorylated state of the RB within a range of 15 to 75 hours, Hoffman teaches administration of as much as 2 grams per day or more of the compositions disclosed therein, which comprise one or more GSH-depleting agents such as curcumin and BSO. Applicants have presented no factual evidence that such administration does not have the effects recited in the instant claims, i.e., there is no evidence of record that administration of a composition comprising curcumin and BSO administered in doses of 2 grams

per day or more would not maintain the dephosphorylated state of the RB within a range of 15 to 75 hours.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26, 36, and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-15, 20, and 25-28 of copending Application No. 11/596,043. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed methods encompass administration of the same combinations of active agents to the same patient populations.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants argue that the present application calls for four agents: disulfiram, curcumin, BCNU, and BSO, whereas the '043 application calls for four agents by function. This is not persuasive because claim 13 of the '043 application explicitly recites the same combination recited in the instant claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/

Primary Examiner, Art Unit 1614

May 10, 2010